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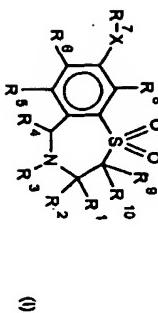
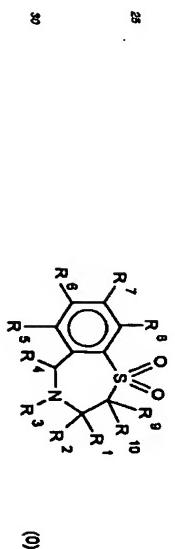
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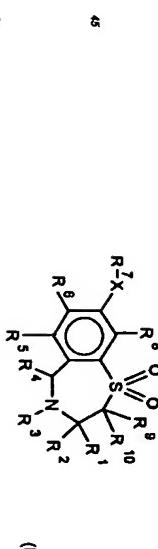
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(54) Hypolipidemic 1,4-benzothiazepine-1,4-diones
(57) The present invention is concerned with new hypolipidemic compounds, with processes and novel intermediates for their preparation, with pharmaceutical compositions containing them and with their use in medicine, particularly in the prophylaxis and treatment of hyperlipidemic conditions, such as atherosclerosis.wherein R¹ to R¹⁰ and X are as defined.(54) Hypolipidemic 1,4-benzothiazepine-1,4-diones
(57) The present invention is concerned with new hypolipidemic compounds, with processes and novel intermediates for their preparation, with pharmaceutical compositions containing them and with their use in medicine, particularly in the prophylaxis and treatment of hyperlipidemic conditions, such as atherosclerosis.

Compounds of the formula (I):



wherein

is a straight chained C₁₋₅ alkyl group;
is a straight chained C₁₋₅ alkoxy group;
is hydrogen or a group OR¹¹ in which R¹¹ is hydrogen, optionally substituted C₁₋₃ alkyl or a C₆-alkoxy group;

The present invention is concerned with new hypolipidemic compounds, with processes and novel intermediates for their preparation, with pharmaceutical compositions containing them and with their use in medicine, particularly in the prophylaxis and treatment of hyperlipidemic conditions, such as atherosclerosis.

Hypolipidemic conditions are often associated with elevated plasma concentrations of low density lipoprotein (LDL) cholesterol and very low density lipoprotein (VLDL) cholesterol. Such concentrations can be reduced by increasing the absorption of bile acids from the intestine. One method by which this may be achieved is to inhibit the bile acid active uptake system in the intestinal lumen. Such inhibition stimulates the conversion of cholesterol to bile acid by the liver and the resulting increase in demand for cholesterol produces a corresponding increase in the rate of clearance of LDL and VLDL cholesterol from the blood plasma or serum.

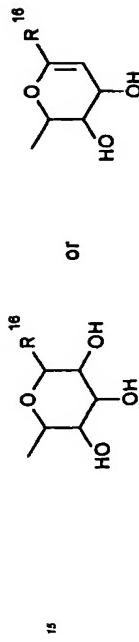
There has now been identified a novel class of heterocyclic compounds which reduce the plasma or serum concentrations of LDL and VLDL cholesterol and in consequence are particularly useful as hypolipidemic agents. By decreasing the concentrations of cholesterol and its ester in the plasma, the compounds of the present invention retard the build-up of atherosclerotic lesions and reduce the incidence of coronary heart disease-related events. The latter are defined as cardiovascular events associated with increased concentrations of cholesterol and cholesterol ester in the plasma or serum.

For the purposes of this specification, a hypolipidemic condition is defined as any condition wherein the total cholesterol concentration (LDL + VLDL) in the plasma or serum is greater than 240 mg/dL (6.21 mmol/L). *J. Amer. Med. Assoc.*, 256, 20, 2846-2858 (1986).

International Patent Application No. WO 86051188 describes compounds of formula (I).

R⁴ is pyridyl or optionally substituted phenyl;
R⁵, R⁶ and R⁸ are the same or different and each is selected from hydrogen, halogen, cyan, R¹⁵-acetylidic,
OR¹⁵, optionally substituted C₁₋₄ alkyl, COR¹⁵, OH(CHR¹⁵)_nRSi, SiO_nRSi, P(O)(OR¹⁵)₂,
OCOR¹⁵, OCF₃, OCN, SCN, NHON, CH₂OR¹⁵, CHO, (CH₂)_pCN, CON(R¹²)₂,
(CH₂)_pCO₂R¹⁵, (CH₂)_pNH⁺R¹²A¹³, CO₂R¹⁵, NSO₂R¹⁵, NHCO₂R¹⁵, OCH₂OR¹⁵,
O(CH₂)_pSO₂R¹⁵, O(CH₂)_pSO₃R¹⁵, O(CH₂)_pNHR¹²A¹³R¹⁴ wherein
is integer from 1-4,
R¹², R¹³, R¹⁴ and R¹⁵ are independently selected from hydrogen and optionally substituted C₁₋₆ alky;

R⁷ is a group of the formula



wherein the hydroxyl groups may be substituted by acetyl or benzyl, or
-(C₁₋₆ alkyl)-R⁷;
wherein the alkyl group may be substituted with one or more hydroxyl groups;
is -COOH, -CH₂-OH, -CH₂O-Acetyl, -COOMe, -COOEt;
is H, -OH, -NH₂, -COOH or COOR¹⁶;
is (C₁₋₄)_palkyl (or -NH-(C₁₋₄)-alkyl);
is -NH+ or -O-; and
X

R⁹ and **R¹⁰** are the same or different and each is hydrogen or C₁₋₆ alky; and salts, solvates, and physiologically functional derivatives thereof.

When **R⁴** is a substituted phenyl group, there may be one to five, preferably one or two substituents which are the same or different and are each selected from halogen, hydroxy, nitro, phenyl-C₁₋₄ alky, optionally substituted C₁₋₄ alkyl, SiO_nRSi, P(O)(OR¹⁵)₂, or (CH₂)_pNH⁺R¹²A¹³R¹⁴ wherein R¹² to R¹⁴, n and p are as hereinbefore defined.

Preferred embodiments of the compounds of formula (I) include compounds of the formula (III), (IV) or (Va)

40

wherein R¹ to R¹⁰ and X are as hereinbefore defined.
When one or more of R³ to R⁸, R⁹ or R¹¹ to R¹⁴ is a substituted C₁₋₆ alkyl group, or comprises a C₁₋₆ silyl group
the substituents may be the same or different and each is selected from hydroxy, halogen, C₁₋₆ alky, C₁₋₆ alkoxy,
CO₂Ar, nitrile, CO₂R²⁰, SO₂R²¹, NR²²R²³, NR²²R²³ wherein R²⁰ to R²³ are the same or different and each is
selected from hydrogen or C₁₋₆ alky.

40 Suitable R¹ is methyl, ethyl or propyl and preferably R¹'s is ethyl. Suitably R² is methyl, ethyl, n-propyl, n-butyl or n-

partly. Preferably R² is n-butyl.

Preferably R³ is hydrogen.

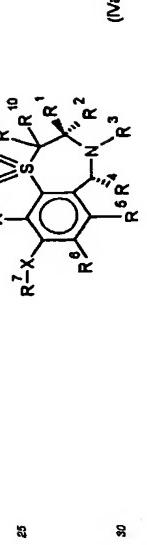
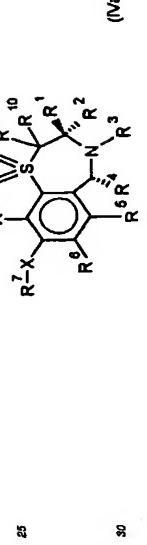
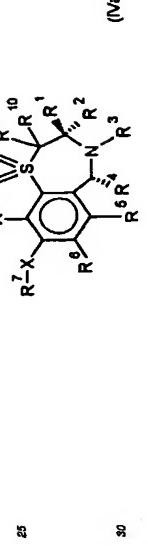
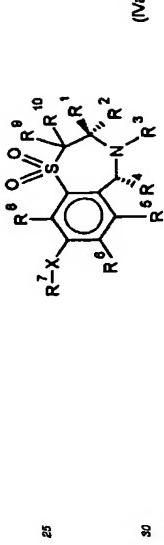
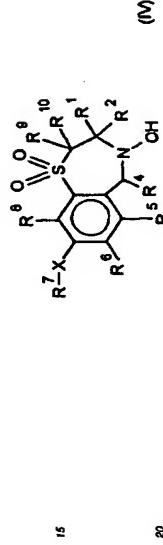
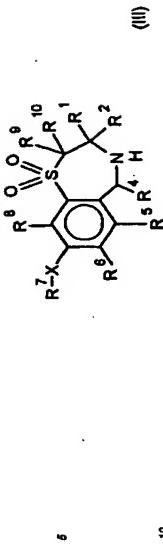
Suitably R⁷ is selected from

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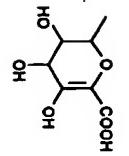
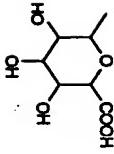
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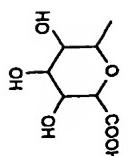


ethyl, methoxy, alphony, trifluoromethyl, hydroxy, carboxy or $O(CH_2)_2SO_3H$. Preferably R^4 is unsubstituted phenyl.

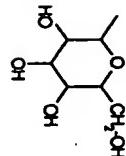
In the compounds of the formula (III), suitably at least one and preferably all of R^9 , R^8 and R^6 are hydrogen. When R^5 , R^6 and R^8 are other than hydrogen then they are suitably C_{1-4} alkyl optionally substituted by fluorine, C_{1-4} alphony, halogen or hydroxyl, most suitably methyl, methoxy, hydroxy, trifluoromethyl or chloro and preferably methoxy, alphony or hydroxyl, most suitably methyl, methoxy, hydroxy, trifluoromethyl or chloro and preferably methoxy, halogen or hydroxyl, most suitably methyl, methoxy, hydroxy, trifluoromethyl or chloro and preferably methoxy. When R^5 , R^6 and R^8 are other than hydrogen then they are suitably C_{1-4} alkyl optionally substituted by fluorine, C_{1-4} alphony, halogen or hydroxyl, most suitably methyl, methoxy, hydroxy, trifluoromethyl or chloro and preferably methoxy. Most preferably, R^1 is *tert*-butyl, R^2 is ethyl, R^3 , R^5 , R^6 , R^8 and R^{10} are hydrogen, R^4 is phenyl and R^7 is



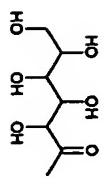
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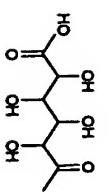
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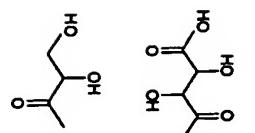
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Pharmaceutically acceptable salts are particularly suitable for medical applications because of their greater aqueous solubility relative to the parent, i.e. basic, compounds. Such salts must clearly have a pharmaceutically acceptable anion or cation. Suitable pharmaceutically acceptable acid addition salts of the compounds of the present invention include those derived from inorganic acids, such as hydrochloric, hydrobromic, phosphoric, metaphosphoric, nitric, sulfuric and sulfonic acids, and organic acids, such as acetic, benzoic, citric, citric, citrate, chabassardic, fumaric, glutamic, glycolic, lactic, laurotic, maleic, methanesulfonic, succinic, propionic, tartaric and trifluoroacetic acids. The chloride salt is particularly preferred for medical purposes. Suitable pharmaceutically acceptable base salts include ammonium salts, alkali metal salts, such as sodium and potassium salts, and alkaline earth salts, such as magnesium and calcium salts.

Salts having a non-pharmaceutically acceptable anion are within the scope of the invention as useful intermediates for the preparation or purification of pharmaceutically acceptable salts and/or for use in non-therapeutic, for example, in vitro, applications.

The term "physiologically functional derivative" as used herein refers to any physiologically acceptable derivative of a compound of the present invention, for example, an ester which upon administration to a mammal, such as a human, is capable of providing (directly or indirectly) such a compound or an active metabolite thereof.

A further aspect of the present invention is products of the compounds of the invention. Such products can be metabolised *in vivo* to give a compound according to the invention. These products may or may not be active in their own right.

The compounds of the present invention can also exist in different polymorphic forms, for example, amorphous and crystalline polymorphic forms. All polymorphic forms of the compounds of the present invention are within the scope of the invention and are a further aspect thereof.

The term "alkyl" as used herein refers, unless otherwise stated, to a monocyclic straight or branched chain radical. Likewise, the term alphony refers to a monocyclic straight or branched chain radical attached to the parent molecule mostly through an oxygen atom. The term "phenylalkoxy" refers to a monovalent phenyl group attached to a divalent C₁₋₅ alkylene group which is itself attached to the parent molecular moiety through an oxygen atom.

The compounds of formula (I) exist in forms wherein the carbon centres -C(R¹)R²- and -CH(R¹)²- are *tert*-butyl. The present invention includes within its scope each possible optical isomer substantially free, i.e. as associated with less than 5%, of any other optical isomer(s), and mixtures of one or more optical isomers in any proportions, including racemic mixtures.

For the purposes of this specification, the absolute chiralities of the aforementioned carbon centres are given in the order -C(R¹)²CH², then -CH(R¹)².

In those cases where the absolute stereochemistry at -C(R¹)R²- and -CH(R¹)²- has not been determined, the compounds of the invention are defined in terms of the relative positions of the R¹/R² and R⁴/R⁵ substituents. Thus those compounds wherein the bulk of the R¹ and R² substituents, i.e. the substituent of higher mass, and the R⁴ substituent are both located on the same side of the phiazepine ring are referred to herein as "cis", and those compounds in which the bulk of the R¹ and R² substituents are located on opposite sides of the ring are referred to as "trans" and are preferred. It will be evident to a skilled person that both cis- and trans-compounds of the invention can each exist in two

Suitably X is O.
Suitably R⁹ and R¹⁰ are hydrogen, methyl or ethyl, hydrogen. Preferably R⁹ and R¹⁰ are both hydrogen.
Suitably R⁴ is pyridyl or phenyl optionally substituted, preferably at the 4- and/or 3-position by halogen, methyl.

enantiomeric forms which are individually designated "(+)" or "(-)" according to the direction of rotation of a plane of polarization when passed through a sample of the compound. Cis or trans compounds of the invention in which the individual enantiomers have not been resolved are referred to herein using the prefix "(±)".

According to further aspects of the invention, there are also provided:

- (a) compounds of formula (I) and pharmaceutically acceptable salts, solvates and physiologically functional derivatives thereof for use as therapeutic agents, particularly in the prophylaxis and treatment of clinical conditions for which a bile acid uptake inhibitor is indicated, for example, a hyperlipidemic condition, such as atherosclerosis;
- (b) pharmaceutical compositions comprising a compound of formula (I) or one of its pharmaceutically acceptable salts, solvates, or physiologically functional derivatives, at least one pharmaceutically acceptable carrier and, optionally, one or more other physiologically active agents;
- (c) the use of a compound of formula (I) or of a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof in the manufacture of a medicament for the prophylaxis or treatment of a clinical condition for which a bile acid uptake inhibitor is indicated, for example, a hypertensive condition, such as atherosclerosis;
- (d) a method of inhibiting the absorption of bile acids from the intestine of a mammal, such as a human, which comprises administering an effective bile acid absorption inhibiting amount of a compound of formula (I) or of a pharmaceutically acceptable salt, solvate, or physiologically functional derivative thereof to the mammal;
- (e) a method of reducing the blood plasma or serum concentrations of LDL and VLDL cholesterol in a mammal, such as a human, which comprises administering an effective cholesterol reducing amount of a compound of formula (I) or of a pharmaceutically acceptable salt, solvate, or physiologically functional derivative thereof to the mammal;
- (f) a method of reducing the concentrations of cholesterol and cholesterol ester in the blood plasma or serum of a mammal such as a human, which comprises administering an effective cholesterol and cholesterol ester reducing amount of a compound of formula (I) or of a pharmaceutically acceptable salt, solvate, or physiologically functional derivative thereof to the mammal;
- (g) a method of increasing the fecal excretion of bile acids in a mammal, such as a human, which comprises administering an effective bile acid fecal excretion increasing amount of a compound of formula (I) or of a pharmaceutically acceptable salt, solvate, or physiologically functional derivative thereof to the mammal;
- (h) a method for the prophylaxis or treatment of a clinical condition in a mammal, such as a human, for which a bile acid uptake inhibitor is indicated, for example, a hyperlipidemic condition, such as atherosclerosis, which comprises administering a therapeutically effective amount of a compound of the formula (I) or of a pharmaceutically acceptable salt, solvate, or physiologically functional derivative thereof to the mammal;
- (i) a method of reducing the incidence of coronary heart disease-related events in a mammal, such as a human, which comprises administering an effective coronary heart disease-related events reducing amount of a compound of formula (I) or of a pharmaceutically acceptable salt, solvate, or physiologically functional derivative thereof;
- (j) a method of reducing the concentration of cholesterol in the blood plasma or serum of a mammal, such as a human, which comprises administering an effective cholesterol reducing amount of a compound of formula (I);
- (k) processes for the preparation of compounds of formula (I) (including salts, solvates and physiologically functional derivatives thereof as defined herein); and
- (l) novel chemical intermediates in the preparation of compounds of formula (I).

(m) the compounds of Synthetic Example 1 to 5 as hereinlater disclosed.

Hereinafter all references to "compound(s)" or formula (I) refer to compound(s) of formula (I) as described above together with their salts, solvates and physiologically functional derivatives as defined herein.
The amount of a compound of formula (I) which is required to achieve the desired biological effect will, of course, depend on a number of factors, for example, the specific compound chosen, the use for which it is intended, the mode

of administration and the clinical condition of the recipient. In general, a daily dose is in the range of from 0.3 mg to 100 mg (rangingly from 3 mg to 50 mg) per day per kilogram bodyweight, for example, 3-10 mg/kg/day. An intravenous dose can, for example, be in the range of from 0.3 mg to 1.0 mg/kg, which can conveniently be administered as an infusion from 10 to 100 mg per kilogram per minute. Infusion fluids suitable for this purpose can contain, for example, from 0.1 mg to 10 mg, typically from 1 mg to 10 mg, per milliliter. Unit doses can contain, for example, from 1 mg to 100 mg and orally administrable unit dose formulations, such as tablets or capsules, may contain, for example, from 1.0 to 1000 mg, typically from 10 to 500 mg. In the case of pharmacaceutically acceptable salts, the weights indicated above refer to the weight of the benzothiazepine ion derived from the salt.

For the prophylaxis or treatment of the conditions referred to above, the compounds of formula (I) can be used as the compound per se, but are preferably presented in an acceptable form of a pharmaceutical composition. The carrier must, of course, be acceptable in the sense of being compatible with the other ingredients of the composition and must not be deleterious to the recipient. The carrier can be a solid or a liquid, or both, and is preferably formulated with the compound as a unit-dose composition, for example, a tablet, which can contain from 0.05% to 95% by weight of the active compound. Other pharmaceutically active substances can also be present including other compounds of formula (I). The pharmaceutical compositions of the invention can be prepared by any of the well known techniques of pharmacy consisting essentially of admixing the components.

Pharmaceutical compositions according to the present invention include those suitable for oral, rectal, topical, buccal (e.g., sub-lingual) and parenteral (e.g., subcutaneous, intramuscular, intradermal, or intravenous) administration, although the most suitable route in any given case will depend on the nature and severity of the condition being treated and on the nature of the particular compound of formula (I) which is being used. Enteric-coated and antibiotic-coated controlled release formulations are also within the scope of the invention. Preferred are acid and gastric juice resistant formulations. Suitable enteric coatings include cellulose acetate, polyvinylacetate phthalate, hydroxypropymethylcellulose phthalate and anionic polymers of methacrylic acid and methacrylic acid methyl ester.

Pharmaceutical compositions suitable for oral administration can be presented in discrete units, such as capsules, cachets, lozenges, or tablets, each containing a predetermined amount of a compound of formula (I); as a powder or granules; as a solution or a suspension in an aqueous or non-aqueous liquid; or as an oil-in-water or water-in-oil emulsion. As indicated, such compositions can be prepared by any suitable method of pharmacy which includes the step of bringing into association the active compound and the carrier which can constitute one or more accessory ingredients. In general, the compositions are prepared by uniformly and intimately admixing the active compound with a liquid or finely divided solid carrier, or both, and then, if necessary, shaping the product. For example, a tablet can be prepared by compressing or moulding a powder or granules of the compound, optionally with one or more accessory ingredients. Compressed tablets can be prepared by compressing, in a suitable machine, the compound in a free-flowing form, such as a powder or granules, optionally mixed with a binder, lubricant, inert diluent and/or surface active/dispersing agent(s). Moulded tablets can be made by moulding, in a suitable machine, the powdered compound maintained with an inert liquid diluent.

Pharmaceutical compositions suitable for buccal (sub-lingual) administration include lozenges comprising a compound of formula (I) in a flavored base, usually sucrose and, acacia or tragacanth, and pastilles comprising the compound of formula (I) preferably isotropic for parenteral administration conveniently comprise sterile aqueous preparations of compound of formula (I), preferably isotropic with the blood of the intended recipient. These preparations are preferably administered intravenously, although administration can also be effected by means of subdermal, intramuscular, or intradermal injection. Such preparations can conveniently be prepared by admiring the compound with water and rendering the resulting solution sterile and isotonic with the blood. Injectable compositions according to the invention will generally contain from 0.1 to 5% w/w of the active compound.

Pharmaceutical compositions suitable for rectal administration are preferably presented as unit-dose suppositories. These can be prepared by admiring a compound of formula (I) with one or more conventional solid carriers, for example, cocoa butter, and then shaping the resulting mixture.

Pharmaceutical compositions suitable for topical application to the skin preferably take the form of an ointment, cream, lotion, paste, gel spray, aerosol, or oil. Carriers which can be used include vaseline, lanoline, polyethylene glycols, alcohols, and combinations of two or more thereof. The active compound is generally present at a concentration of from 0.1 to 15% w/w of the composition. Such patches can conveniently be prepared by admiring the compound with water and rendering the resulting solution sterile and isotonic with the blood. Injectible compositions according to the invention will generally contain from 0.1 to 5% w/w of the active compound.

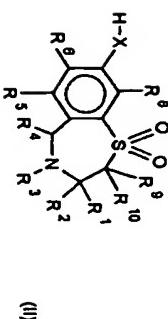
Pharmaceutical compositions suitable for transdermal administration can be presented as discrete patches adapted to remain in intimate contact with the epidermis of the recipient for a prolonged period of time. Such patches suitably contain the active compound in an optionally buffered aqueous solution, dissolved and/or dispersed in a polymer. A suitable concentration of the active compound is about 1% to 30%, preferably about 3% to 15%. As one particular possibility, the active compound can be delivered from the patch by electrotransport or iontophoresis, for example, as described in Pharmaceutical Research, 2(6), 318.

(1980).

ପରେ କୋଣାର୍କ ଦେଖିବାକୁ ଆମେ ଯାଏନ୍ତିରେ କିମ୍ବା କିମ୍ବା କିମ୍ବା

For simplicity, consider first of all cases where α is measured by a process which compares

A) REGULATIONS



by standard procedures (e.g. with N,N -carbonyldiimidazole) at the -X-H group.

Q

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- isolation or a compound or formula (ii) by standard procedures at the X-H group.
- precipitation or glucosidation, a compound of formula (ii) at the X-H group, especially using the imidate method and
- cleavage of protecting groups, especially of hydroxyl and amino functional groups, e.g. acetyl by hydrolysis, benzyl by hydrogenolysis.

The compounds of formula (IV) can be prepared according to the method of preparation disclosed in WO 96/05188.

The compounds of formula (I) substantially free, or other optical isomers can be obtained either by chiral synthesis, for example, by the use of the appropriate chiral starting material(s), such as the aziridine, or by resolution of the prod-

ucts obtained from achiral syntheses, for example, by chiral hptc or by classical resolution with chiral acids.

A corresponding acid addition salt may be effected by reaction with a solution of the appropriate acid, for example, one of those recited earlier. Optional conversion of a compound of formula (1) comprising an acidic substituent to a corre-

spending base salt may be effected by reaction with a solution of the appropriate base, for example, sodium hydroxide. Optional conversion to a physiologically functional derivative, such as an ester, can be carried out by methods known

to those skilled in the art or obtainable from the chemical literature.

methods known or available from the literature to those skilled in the art, for example by alkylation of a hydroxy group.

WO 98/5188:

out by means of three genetically modified cell lines. These were derivatives of the generally known "Chinese hamster ovary" (CHO) cell line, which on account of homologous recombination exclusively produced sodium-fluorescein

be used (concentration) or use most unsophisticated or no human (strain). Gene gun (gene delivery) and magnetic vector delivery are other methods used to introduce recombinant genes into the target cells. All plasmids were based on the standard pCMVneo vector which as important elements has promoter of the human. All plasmids were based on the standard pCMVneo vector which as important elements has promoter of the human. All plasmids were based on the standard pCMVneo vector which as important elements has promoter of the human.

The results showed that the amount of the ribosomal RNA (rRNA) was total RNA resistance against the substances 3418.

The starting material for the production of the present and the next paper concerning the influence of these two *in vitro* methods on the terminal team of the rabbit. From this by means of an RT-PCR procedure (reverse transcriptase reaction, followed

5'-acetyltaurathio-*β*-alanylarginine-3', a C12NA was synthesized which contained the total protein- κ -coupling region or one RIBAT, and also 41 base pairs on the 5'-adjacent and 31 base pairs on the 3'-adjacent untranslated region. This region

was digested by cleavage sites for the restriction enzymes KpnI (at the 5'-end) and XbaI (at the 3'-end). The outcomes of cDNA and DNA of plasmid pCDNA1neo were digested using the two restriction enzymes mentioned and resulting frag-

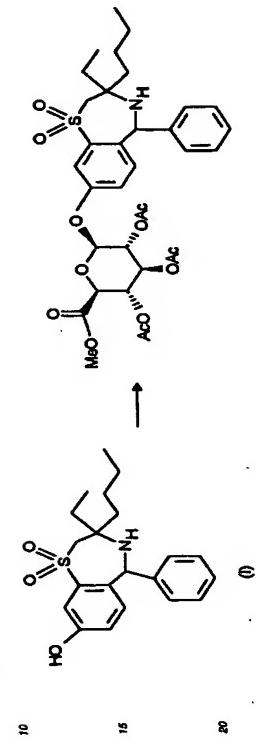
ments were contaminated by means or ingests to give the expression plasma protein.

Example 3 Example 11 of WO 96/05188	I_{C50} (RIBAT) I_{C50} (RIBAT)	70 nM = 0,07 μ M
		4 μ M

this, the $[C_{50}]$ value determined with the cell line CHO-LBATS was several powers of ten higher. This shows that compounds according to the invention can exert a comparable effect on orthologous sodium-dependent stilic acid transporters of various species and, in contrast to this, the effect on paralogous transporters of other organs can be very much smaller.

For a better understanding of the invention, the following Example is given by way of illustration and is (e.g. with N,N -carbonyldiimidazole) not to be construed in any way as limiting the scope of the invention.

Example 1



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To a solution of 2.9 g methyl-2,3,4-trichloroacetimidate in 100 ml dry dichloromethane at room temperature under Argon is added 4.6 ml trichloroacetonitrile and the solution was stirred for 10 min. Then 750 mg potassium carbonato is added. After 30 min of stirring at room temperature the mixture is filtered through a short pad of silica, eluting with ether. The filtrate is concentrated *in vacuo* to yield the crude product as a pale yellow solid (3.7 g). 10 g of this product were dissolved in 15 ml dry dichloromethane and added to a solution of Phenol I (trans racemate) in 30 ml dry dichloromethane. After cooling to -10°C 0.32 ml $BF_3 \cdot OEt_2$ were added and after 30 min at -10°C the mixture was stirred for 20 h at room temperature. Then the reaction was diluted with dichloromethane and washed with aqueous sodium bicarbonate and brine. The combined organic phases were dried over Na_2SO_4 and evaporated *in vacuo*. The crude product was purified by silica gel chromatography (n-heptane/ethyl acetate, 2:1) to obtain 825 mg of Example 1.

$R_f = 0.17$ (n-heptane/ethyl acetate 1:1).

$C_{34}H_{34}NO_2S$ (689); MS (FAB, 3-NBA): 690 ($M+H^+$)

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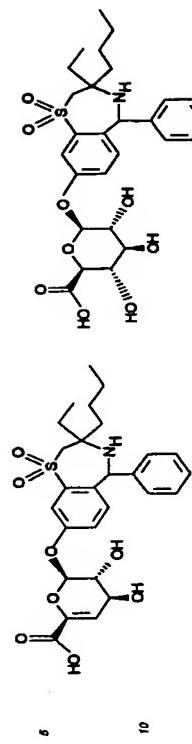
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Example 2



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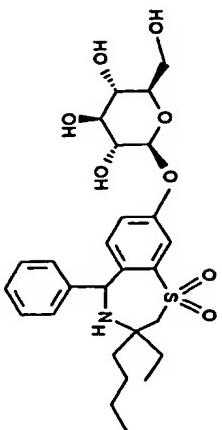
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Example 5

EP 0 664 582 A2
(continued)

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Example 5 was obtained in analogy to example 2

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 $R = 0.20 \text{ (CH}_2\text{CH}_2\text{MOH)}_{33} \text{ % eq. NH}_3; 60:60:13$
 $\text{C}_{27}\text{H}_{35}\text{NO}_3\text{S}$ (55); MS (FAB, 3-NBA); 536 (M+H⁺)

NMR Data of Example 3

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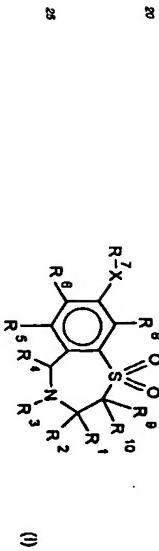
Chemical Shifts in MeOD-D_6 at 300 K

Position	Isomer A ¹ H	Isomer B ¹ H	Isomer A ¹³ C	Isomer B ¹³ C
20	-	-	-	-
1	3.50/3.14	3.50/3.18	58.51	58.51
2	-	-	64.63	64.63
3	-	-	142.39	142.39
4	-	-	140.61	140.61
5	6.00	6.01	.55.74	.55.74
6	1.57/1.44	1.57/1.44	34.39	34.38
7	0.88	0.88	7.94	7.94
8	2.22/1.79	2.22/1.79	31.95	31.95
9	1.17	1.17	26.22	26.22
10	1.28	1.28	24.06	24.06
11	0.81	0.81	14.31	14.31
12	-	-	143.98	143.98
13	7.39	7.39	120.05	120.05
14	7.38	7.38	129.38	129.38
15	7.29	7.29	120.09	120.09
16	6.81	6.81	131.10	131.10
17	7.17	7.17	121.72	121.72
18	-	-	157.69	157.69
19	7.72	7.73	117.81	117.81

15 Claims

1. A compound of the formula (I)

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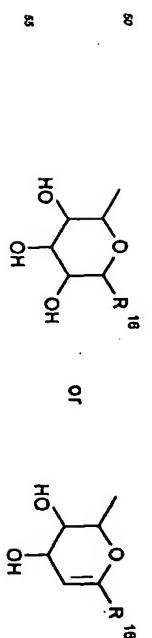
wherein

R^1 , R^2 , R^3 , R^4 , R^5 , R^6 and R^9 is a straight chained C₁₋₄ alky group; is a straight chained C₁₋₄ alkoxy group; is hydrogen or a group OR¹¹ in which R¹¹ is hydrogen, optionally substituted C₁₋₄ alkyl or C₁₋₄ alkoxy group; is pyrrolidinyl or optionally substituted phenyl; are the same or different and each is selected from hydrogen, halogen, cyano, R¹⁵, acyl, OR¹⁵, optionally substituted C₁₋₄ alky, COR¹⁵, CNOR¹⁵, Si(O_nR¹⁵)₃, CON(R¹⁵)₂, OCOR¹⁵, SCN, NH₂, CH₂OR¹⁵, CHO, (CH₂)_nCN, CON(R¹⁵)₂, (CH₂)_nCOOR¹⁵, CO₂R¹⁵, NHCOOF₃, NHSO₃R¹⁵, OCH₂OR¹⁵, OCH₂CHR¹⁵, O(CH₂)_nOR¹⁵, O(CH₂)_nCHR¹⁵ and O(CH₂)_nNR¹⁵RF₁₄; wherein R¹⁵ is an integer from 1-4.

R^6 is an integer from 0-3 and is independently selected from hydrogen and optionally substituted C₁₋₄ alky;

R^7 , R^8 , R^9 and R^{10} is a group of the formula

P or
 n , R^{11} , R^{12} , R^{13} and R^{14} are independently selected from hydrogen and optionally substituted C₁₋₄ alky;



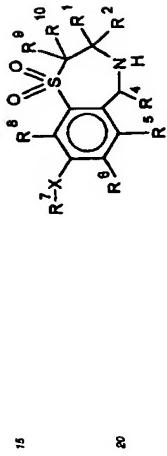
R^7 , R^8 , R^9 and R^{10} is a group of the formula

wherein the hydroxyl groups may be substituted by acetyl or benzyl, or
 $-(C_1-C_6\text{-alkyl})-R^7$

wherein the alkyl group may be substituted with one or more hydroxyl groups;
 is -COOH, -CH₂-OH, -CH₂O-Acetyl, -COOMe or -COOEt
 is H, -OH, -NH₂, -COOH or COOR¹⁸,
 is (C₁-C₆-alkyl) or -NH-(C₁-C₆-alkyl);
 is -NH- or -O-; and

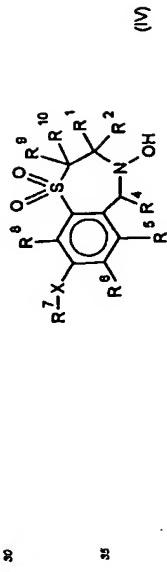
¹⁰ R⁹ and R¹⁰ are the same or different and each is hydrogen or C₁-4 alky, and salts, solvates, and physiologically functional derivatives thereof.

2. The compounds as claimed in claim 1 which are of the formula (III)



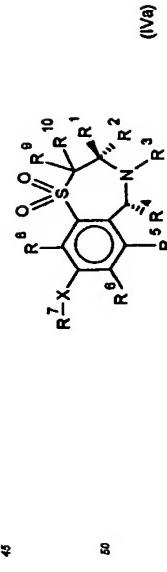
²⁵ wherein R¹ to R¹⁰ and X are as defined in claim 1.

3. The compounds as claimed in claim 1 which are of the formula (IV):



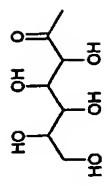
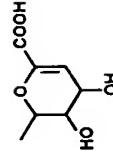
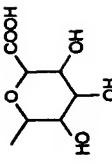
⁴⁰ wherein R¹ to R¹⁰ and X are as defined in claim 1.

4. The compounds as claimed in claim 1 which are of the formula (IVa)



⁵⁵ wherein R¹ to R¹⁰ and X are as defined in claim 1.

5. A compound according to any of the claims 1 to 4 wherein R⁷ is selected from



prises, administering to a mammal an effective bile acid uptake inhibition amount of a compound according to any of the claims 1 to 6.



- 5 10. A method of treating a hyperlipidemic condition in a mammal which comprises, administering to the mammal an effective hyperlipidemic treatment amount of a compound according to any of the claims 1 to 8.
11. The method of claim 10 wherein the hyperlipidemic condition is atherosclerosis.



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- 10 12. Use of a compound according to any one of claims 1 to 8 or a pharmaceutically acceptable salt, solvate, or physiologically functional derivative thereof in the manufacture of a medicament for the prophylaxis or treatment of a clinical condition for which a bile uptake inhibitor is indicated.

- 11 13. A method for the preparation of a compound according to any one of the claims 1 to 8 and salts, solvates, and physiologically functional derivatives thereof, which comprises

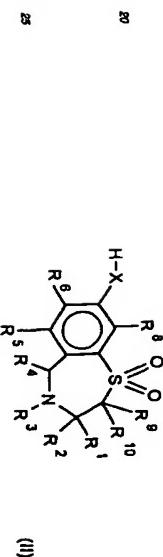
- 15 a) cyclization of a compound of formula II



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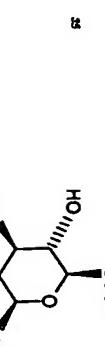
and X is O.

17 30. A compound of the formula

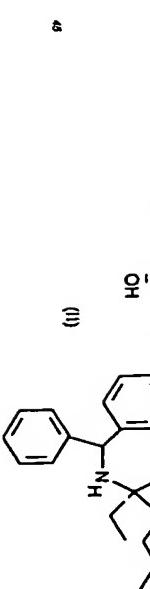


31 by standard procedures at the -X-H group

- 32 or
33 a) alkylation a compound of formula II by standard procedures at the -X-H group
or
34 a) glycosylation or glutamidation a compound of formula II at the -X-H group, and
b) cleavage of protecting groups, especially of hydroxy and amino functional groups.



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7. A pharmaceutical composition comprising one or more compounds according to any of the claims 1 to 6.

- 65 8. A acid and gastric juice resistant pharmaceutical composition comprising one or more compounds according to any of the claims 1 to 6.
9. A method of treating a clinical condition in a mammal for which a bile acid uptake inhibitor is indicated which com-



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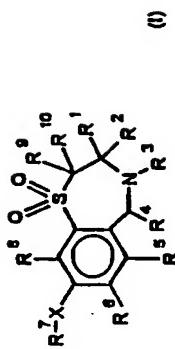
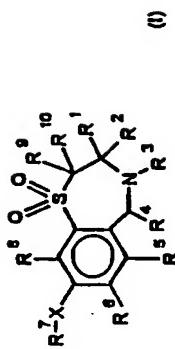
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65329 Frankfurt am Main (DE)	• Stengelin, Siegfried, Dr.
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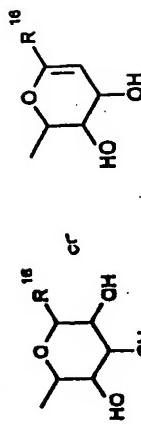
(54) Hypolipidemic 1,4-benzothiazepine-1,4-dioxides

(57) The present invention is concerned with new hypolipidemic compounds (I) and with their use in medicine, particularly in the prophylaxis and treatment of hyperlipidemic conditions, such as atherosclerosis.
Compounds of the formula (I):



wherein X is -NH- or -C=; and

R⁷ is a group of the formula



wherein the hydroxyl groups may be substituted by acetyl or benzyl, or

(Cont. next page)

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DOCUMENTS CONSIDERED TO BE RELEVANT	
Category	Description of document which is relevant, where appropriate.
X	WO 93 16055 A (THE WELLCOME FOUNDATION LIMITED) 19 August 1993 * the whole document
X	WO 91 18183 A (THE WELLCOME FOUNDATION LIMITED) 18 August 1994 * the whole document
X	WO 91 18184 A (THE WELLCOME FOUNDATION LIMITED) 18 August 1994 * the whole document
D,A	WO 95 05188 A (THE WELLCOME FOUNDATION LIMITED) 22 February 1996 * the whole document

INCOMPLETE SEARCH	
The following documents have been found which may be relevant to the subject matter of the application. However, they have not been examined in detail and it is not known whether they contain all the relevant information. It is recommended that you make your own detailed examination of these documents.	Reason for the limitation of the search:
Claims examined in part only:	Claims not examined.
Other search results incomplete:	Other search results incomplete.
Other not mentioned:	Other not mentioned.

Place of search	Date of completion of the search	Examiner
THE HAGUE	9 June 1998	Allard, M
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V. particularly relevant to claims above	I. of interest or relevance, but not particularly relevant to the claims above	
A. relevant to other parts of the application	II. relevant to other parts of the application	
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